The Utility of Intraoperative Bilateral Internal Jugular Venous Sampling With Rapid Parathyroid Hormone Testing

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Objective: To determine the utility of routine perioperative bilateral internal jugular venous sampling of parathyroid hormone (BIJ PTH) for localization during parathyroid surgery.

Summary Background Data: Venous sampling for PTH is a useful tool for parathyroid localization in patients undergoing reoperative surgery for hyperparathyroidism (HPT). With the development of intraoperative rapid PTH (ioPTH) testing, internal jugular PTH sampling with ioPTH testing to guide operative localization has been shown to be possible in select, difficult cases. However, the value of BIJ PTH for patients with HPT is unclear.

Methods: Between May 2004 and February 2006, 216 consecutive patients underwent neck exploration for HPT by one surgeon. Of these, 168 patients had BIJ PTH. Internal jugular venous blood was drawn from both left and right sides and analyzed for PTH using a rapid PTH assay. BIJ PTH levels were defined as lateralizing if >5% differences were observed between the right and left internal jugular vein samples.

Results: Of the 168 patients, 120 (71.4%) had a single parathyroid adenoma, 15 (8.9%) had double adenoma, and 33 (19.6%) had hyperplasia. The cure rate after parathyroidectomy was 98.2%. There were no complications related to BIJ PTH sampling. Sensitivity and positive predictive value of BIJ PTH for primary hyperparathyroidism were 80% and 71%, respectively. BIJ PTH was diagnostic in 95 cases (62.9%) in primary HPT. BIJ PTH successfully localized an abnormal gland in 26 of 45 (57.8%) in patients with negative sestamibi scanning. BIJ PTH was especially helpful in 18 of 168 (10.7%) cases when intraoperative peripheral parathyroid hormone did not fall by 50% and BIJ PTH successfully localized the hyperfunctioning glands.

Conclusions: In patients with HPT, BIJ PTH is safe and effective, providing additional localization information in the majority of cases. BIJ PTH is particularly useful in the setting of negative sestamibi scanning and in complex multigland disease cases.

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Surgical intervention remains the only curative therapy for patients with hyperparathyroidism. For many years, bilateral neck exploration with resection of enlarged parathyroid gland(s) was the standard operation performed for HPT and is associated with a greater than 95% cure rate and minimal morbidity in the hands of an experienced endocrine surgeon.[1–3] Although there are several perioperative adjuncts including Tc-99m sestamibi scanning,[4,5] radioguided surgery,[2,6–9] and selective venous sampling for parathyroid hormone (PTH) to localize hyperfunctioning parathyroid gland,[3,10,11] there is a variation in the quoted sensitivity of each of these techniques.[12] Of these, selective venous sampling was found to be useful to localize recurrent or persistent hyperparathyroidism.[11] With the development of intraoperative peripheral PTH testing (ioPTH),[13–15] PTH can be measured during parathyroid surgery. Some surgeons have reported internal jugular PTH sampling with ioPTH testing to guide operative localization was feasible.[16,17] However, the accuracy of bilateral internal jugular (BIJ) PTH for patients with hyperparathyroidism is unclear because of the lack of data in a large group of patients. Therefore, the purpose of this study was to determine the utility of routine perioperative bilateral internal jugular venous sampling of PTH (BIJ PTH) for localization during parathyroid surgery.

METHODS

Between May 2004 and February 2006, 216 consecutive patients underwent neck exploration for hyperparathyroidism by one surgeon (H.C.) at the University of Wisconsin. Of these, 168 patients had BIJ PTH. In the operating room, internal jugular venous blood was drawn from both left and right sides percutaneously using 23- to 25-G needle and 3 mL syringe without ultrasound guidance after induction of general anesthesia (before surgical incision). In some cases, BIJ venous blood was drawn through the incision intraoperatively and analyzed for PTH using a rapid PTH assay (Elecsys 1010 or 2010). The results of the BIJ PTH sampling were available and used by the surgeon in all 168 cases in this study. The analysis for the utility of the technique was performed postoperatively once the etiology of the HPT was identified.

BIJ PTH levels were defined as lateralizing if >5% differences were observed between the right and left internal jugular vein samples. In our initial experience with BIJ PTH sampling, we observed that a difference of 5% to 10% was consistent with a unilateral adenoma. After analyzing the data

from these subsequent 168 patients, it became clear to us that a >5% difference was more appropriate.

The following definitions were used for calculating the sensitivity and positive predictive value for BIJ PTH sampling. True positive was when one side of IJ PTH was 5% greater than the other side of IJ PTH and the operative findings concurred. True negative was when there were less than 5% differences between BIJ PTH, and there were multiple bilateral hyperfunctioning parathyroid glands found at surgery. A false positive was when one side of IJ PTH was 5% greater than the other side of IJ PTH, whereas the operative findings revealed multiple bilateral gland disease or contralateral hyperfunctioning glands. A false negative was when there were less than 5% differences between BIJ PTH, but unilateral hyperfunctioning glands were found at surgery. The definitions for calculating the sensitivity and positive predictive value for sestamibi scanning were followed as we previously reported.[12]

The definition of single gland disease, double adenomas, and hyperplasia was defined as follows. All resected glands had histopathological identification of hypercellularity to confirm that they were abnormal. In the case of single adenomas, this was defined as a drop of >50% in intraoperative PTH (dynamics) after resection of a single parathyroid gland and biochemical cure postoperatively. Multigland disease was defined by the presence of multiple enlarged, hypercellular glands, but not necessarily by PTH dynamics.

All 168 patients had intraoperative PTH testing. We have previously described our protocol for intraoperative PTH testing and interpretation at the University of Wisconsin.[12,18] All PTH levels were analyzed on the Elecsys 1010 or 2010 machine. As we previously reported, our criteria for a curative resection is a >50% drop in intraoperative PTH levels compared with baseline at 5, 10, or 15 minutes.[12,18] We did not use frozen section analysis during parathyroid surgery to confirm the identity of the resected parathyroid tissue.

All data were recorded prospectively. Surgical cure was defined as a serum calcium level <10.2 mg/dL at least 6 months after surgery. Recurrence was defined as a serum calcium level exceeding 10.2 mg/dL in consecutive samples 6 months after surgery. Persistent disease was defined as a serum calcium level greater than 10.2 mg/dL within 6 months of surgery. Data were recorded as mean ± SEM. Statistical analysis was performed with SPSS software (SPSS Inc.). Statistical significance was defined as a $P < 0.05$.

RESULTS

Patient Data

The mean age was 59 ± 1 years (range, 26–87 years). The mean preoperative calcium and intact PTH levels were 11.0 ± 0.1 mg/dL and 194 ± 29 pg/mL, respectively.

Operative Findings and Outcomes

All of the 168 patients underwent successful intraoperative bilateral internal jugular venous sampling, and there were no intraoperative or postoperative complications related to BIJ PTH sampling (Table 1). Of the 168 patients, 152 (90.4%) had primary HPT, 6 (3.6%) had secondary HPT, and 10 (6.0%) had tertiary HPT. Of the 168 patients, 120 (71.4%) had single adenoma, 15 (8.9%) had double/triple adenoma, and 33 (19.6%) had hyperplasia. The mean postoperative calcium and intact PTH levels were 9.3 ± 0.1 mg/dL and 49.5 ± 3.3 pg/mL, respectively. Therefore, the overall cure rate after parathyroidectomy in this single surgeon series was 98.2% (165 of 168).

TABLE 1. Operative Data

Characteristic	Value
No.	168
Etiology [no. (%)]	
Primary hyperparathyroidism	151 (89.9)
Secondary hyperparathyroidism	6 (3.6)
Tertiary hyperparathyroidism	11 (6.5)
Single adenoma	120 (71.4)
Double/triple adenoma	15 (8.9)
Hyperplasia	33 (19.6)
Postop. serum calcium (mg/dL) (mean ± SEM)	9.3 ± 0.1
Postop. intact parathyroid hormone (pg/mL) (mean ± SEM)	49.5 ± 3.3
Cure rate after parathyroidectomy [no. (%)]	165/168 (98.2)
Complications related to BIJ PTH	0

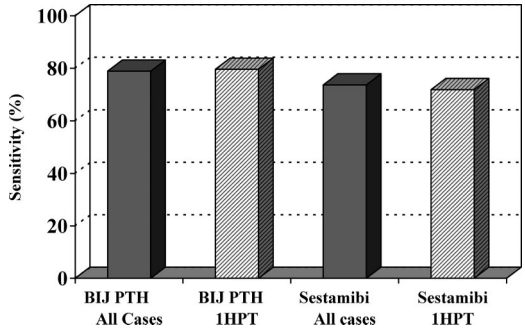

FIGURE 1. Sensitivities of bilateral internal jugular PTH sampling and sestamibi scanning for all cases and primary hyperparathyroidism (1HPT).

Sensitivity and Positive Predictive Value of the BIJ PTH Sampling for Hyperfunctioning Glands

Sensitivities of the BIJ PTH sampling were high for all cases (78.9%) and for patients with primary hyperparathyroidism (79.6%) (Fig. 1), which were higher than those of sestamibi scanning, 73.7% and 71.9%, respectively. Positive predictive values of BIJ PTH were 66.7% for all cases and 70.7% for primary HPT (Fig. 2), which were comparable with those of sestamibi scanning, 79.1% and 79.6%, respectively. Interestingly, the sensitivity of BIJ PTH sampling was significantly higher for upper gland disease (90.1%) than for lower gland disease (66%) ($P < 0.05$) (Fig. 3).

Intraoperative Diagnostic Efficacy of BIJ PTH Sampling

Overall BIJ PTH was diagnostic in 95 cases (62.9%) of primary HPT (Table 2). Of these, BIJ PTH successfully

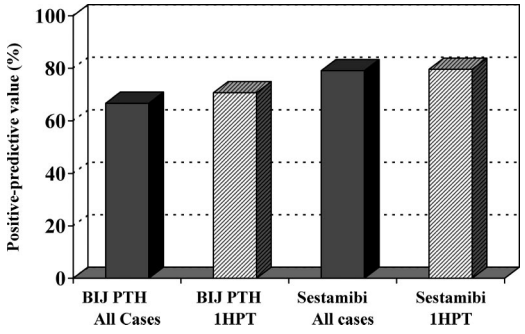

FIGURE 2. Positive-predictive values of bilateral internal jugular PTH sampling and sestamibi scanning for all cases and primary hyperparathyroidism (1HPT).

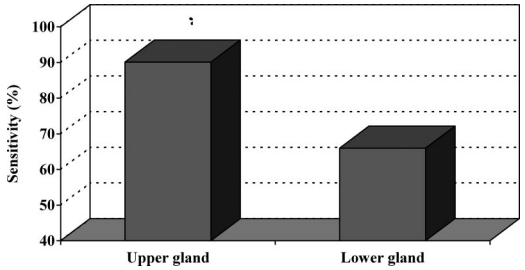

FIGURE 3. Sensitivities of bilateral internal jugular PTH sampling for upper gland adenoma/hyperplasia, lower gland adenoma/hyperplasia. *$P < 0.05$ comparing upper gland adenoma/hyperplasia with lower gland adenoma/hyperplasia.

TABLE 2. Diagnostic Efficacy of BIJ PTH for Primary Hyperparathyroidism

Characteristic	Value [no. (%)]
Diagnostic	95/151 (62.9)
BIJ PTH localized single adenoma and sestamibi false negative	26/151 (17.2)
BIJ PTH localized single adenoma and sestamibi false positive	13/151 (8.6)
BIJ PTH confirmed single gland disease with positive sestamibi	51/151 (33.8)
BIJ PTH confirmed bilateral gland disease with negative sestamibi	5/151 (3.3)
Nondiagnostic	56/151 (37.1)
BIJ PTH nonlocalized and sestamibi true positive	35/151 (23.2)
BIJ PTH nonlocalized and sestamibi false negative, false positive, or not obtained	7/151 (4.6)
BIJ PTH localized in the setting of bilateral gland disease	4/151 (2.6)
BIJ PTH localized wrong site and sestamibi negative or not obtained	10/151 (6.6)

localized a hyperfunctioning gland in the setting of false negative sestamibi scanning in 26 cases (17.2%), and when sestamibi scanning localized opposite site (false positive) in 13 cases (8.6%). BIJ PTH confirmed single adenoma with true positive sestamibi scanning in 51 cases (33.8%), and bilateral gland disease with true negative sestamibi scanning in 5 cases (3.3%). BIJ PTH was nondiagnostic in 56 cases (37.1%) of primary HPT. Of these, there were 10 cases (6.6%) in which BIJ PTH was falsely positive in the setting of negative sestamibi scanning or no preoperative imaging study. BIJ PTH for secondary/tertiary hyperparathyroidism was not as useful as that for primary hyperparathyroidism (Table 3).

TABLE 3. Diagnostic Efficacy of BIJ PTH for Secondary/Tertiary Hyperparathyroidism

Characteristic	Value [no. (%)]
Diagnostic	6/17 (35.2)
Nondiagnostic	11/17 (64.8)

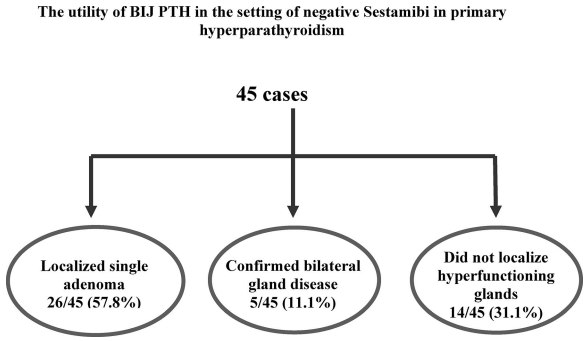

FIGURE 4. Outcomes of patient with primary hyperparathyroidism who had negative preoperative sestamibi scanning.

Utility of BIJ PTH in the Setting of Negative Sestamibi in Primary HPT

We had 45 cases in which patients with primary HPT had preoperative negative sestamibi scanning. Of these 45 patients, BIJ PTH successfully localized in 26 cases (57.8%) and confirmed bilateral gland disease in 5 cases (11.1%) (Fig. 4).

Diagnostic Efficacy of BIJ PTH for Complex Cases

BIJ PTH was especially helpful in 18 cases (10.7%) when intraoperative peripheral parathyroid hormone did not fall by 50% and BIJ PTH successfully localized the hyperfunctioning glands.

Likelihood of Finding Hyperfunctioning Glands if Both BIJ PTH and Sestamibi Scanning Localized Same Site

Both BIJ PTH and sestamibi scanning were performed in 144 cases of primary HPT. Of 144 cases, there are 56 cases in which both BIJ PTH and sestamibi scanning localized the same site. There was only 1 case (1.8%) in which the hyperfunctioning gland was not present in localized site. This suggests that if the sestamibi and BIJ PTH localization studies localize same site, hyperfunctioning glands were found in this site in 55 of 56 (98.2%) cases. Of these 55 patients, we found single adenoma in 51 cases (91.1%) in localized side. In 4 patients (7.1%), we found hyperfunctioning gland in localized side and found additional hyperfunc-

tioning gland in opposite site because intraoperative peripheral parathyroid hormone did not fall by 50%. This indicates that intraoperative peripheral PTH levels are still valuable to confirm surgical cure.

DISCUSSION

The role of perioperative BIJ PTH for localization during parathyroid surgery has not been completely investigated. Preoperative selective and super selective venous sampling for PTH is useful for parathyroid localization for reoperative surgery for hyperparathyroidism.[10,11] However, it is an expensive and invasive procedure, which cannot be done routinely. It has possible complications such as allergic reactions and renal dysfunction related to intravenous contrast, and local vascular complications including hematoma formation, arteriovenous fistula, pseudoaneurysm, thrombosis, and wound infection. With the development of ioPTH,[3,13–15] parathyroid function in each side of the neck can be directly evaluated during surgery for hyperparathyroidism. BIJ venous blood can be easily obtained percutaneously. We had no complications related to the BIJ PTH sampling, including hematoma formation, wound infection, carotid injury, or stroke.

Recent improvements in parathyroid imaging techniques have led to an increase in minimally invasive parathyroidectomy for patients with primary HPT.[4,19,20] Localization technique includes Tc-99m sestamibi scanning, radioguided surgery, and selective venous sampling for PTH. Of these, sestamibi scanning has been considered to be the best imaging modality to localize parathyroid adenoma.[3,4] However, most large studies report sensitivities ranging between 70% and 90%, which is not perfect.[12] To maximize the number of patients who can be offered less invasive procedure, we investigated the value of BIJ PTH for localization. BIJ PTH has high sensitivities ranging 78% to 80%, which is higher than that of sestamibi scanning ranging from 71% to74%. Positive predictive value of BIJ PTH was comparable to that of sestamibi scanning. We found that positive predictive value depends on etiology, and unilateral gland disease in primary HPT patients has higher positive predictive value of 75.2%. However sestamibi still has the main advantage since it can localize ectopically located glands in the lower neck and mediastinum, which are usually missed by BIJ PTH sampling. Importantly, a sestamibi identifying a mid to lower mediastinal parathyroid adenoma would change the operative approach in our institution from a neck incision to a video-assisted thoracoscopic approach.[21,22]

BIJ PTH was diagnostic in the majority of cases for primary HPT (62.9%). We have only 10 cases (6.6%) in which we were misguided by BIJ PTH when BIJ PTH localized wrong site in the setting of false negative or not obtained sestamibi scanning. Diagnostic efficacy of BIJ PTH was not high in patients with secondary/tertiary hyperparathyroidism. Most of these patients were expected to have bilateral gland disease and did not need preoperative localization.

We reviewed the 23 cases of primary HPT in which BIJ PTH did not localize a single adenoma (false negatives). The majority of these undetected single adenomas were lower glands (19 cases). This is consistent with the data shown in Figure 3, indicating that BIJ PTH is more sensitive for superior parathyroid adenomas. We hypothesize that this is because the superior gland more frequently drains into the IJ vein. Based on these results, we try to obtain venous blood from the lowest position possible on the internal jugular vein. Furthermore, 6 of the 23 nonlocalized adenomas were ectopically located (intrathyroidal, n = 1; retroesophageal, n = 2; thymic, n = 4).

We were particularly interested in evaluating the utility of BIJ PTH in the setting of negative preoperative sestamibi scanning, in which BIJ PTH successfully localized 26 of 45 (57.8%) cases. This result indicates that BIJ PTH can provide additional localizing information for the patients with a negative sestamibi scan. Thus, these patients can be offered minimally invasive parathyroidectomy. If both sestamibi scanning and BIJ PTH localized the same site, hyperfunctioning glands were most likely found in localized site in 55 of 56 cases (98.2%) and positive predictive value of concordance was 91.1%.

We also retrospectively reviewed the efficacy of ultrasound in this patient population. Ultrasound was performed in 26 of 168 cases (15.5%). The sensitivity was 47.3% and positive predictive value was 64.2%. There were only 10 cases in which sestamibi scanning, ultrasound, and BIJ PTH were concordant. Five patients in this series had negative sestamibi scan and underwent ultrasound evaluation. In all 5 of these cases, ultrasound did not detect the abnormal parathyroid while BIJ PTH testing did. However, since ultrasound was only used in a select number of patients in this series, it is difficult to make definite conclusions comparing its accuracy to BIJ PTH testing.

In this study, we found that BIJ PTH was especially helpful in 18 (10.7%) cases when intraoperative peripheral parathyroid hormone did not fall by 50% and BIJ PTH successfully localized the hyperfunctioning glands. Of these, all 18 cases were multigland disease: 4 patients were undergoing a reoperative procedure and 6 had ectopic glands (undescended, n = 1; intrathyroidal, n = 1; retroesophageal, n = 2; thymic, n = 2).

We found slight differences in baseline PTH value when comparing the peripheral PTH values to the BIJ ones. In the presence of a single adenoma, the ipsilateral IJ PTH value was significantly higher than the peripheral one. However, in the case of bilateral gland disease, the IJ PTHs tended to also be higher than peripheral levels. Since we did not sample from BIJs after parathyroid resection, we cannot comment on which site would be most appropriate for intraoperative PTH monitoring.

CONCLUSION

This study is the largest to date which prospectively investigated the value of BIJ PTH sampling for localization during parathyroid surgery for HPT. BIJ PTH sampling was safe and effective, providing additional localization information in the majority of cases. BIJ PTH is particularly useful in the setting of negative sestamibi scanning and in complex multigland disease cases.

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